with alcohol. The soft reddish-black waxy extract was sent to our laboratory, where it was fractionally distilled at low pressure, differentially extracted, picrated, and crystallized. The whole process required some hundreds of test-tube pilot tests followed by preparation on a larger scale, designed to produce enough material for tests on mice. The two guides used throughout the work were, of course, the fluorescence spectrum and the assay of carcinogenic potency by application to the skin of mice. The various fractions showed a correspondence between the intensity of the Schroeter bands and the carcinogenic potency. By the autumn of 1931 about 7 g. of a yellow crystalline powder melting at 116° had been accumulated, which showed both high carcinogenic potency and powerful fluorescence in the spectral position required. The process by which this compound was tracked down is illustrated by a fine series of photographs of spectra in Hieger's later paper (1937). Without the clue provided by Mayneord's introduction of the fluorescence spectrum the testing for carcinogenic power upon mice of every crystalline fraction which one could isolate from pitch would have been an almost endless task, and even when a pure crystalline carcinogen had been isolated there would have been nothing to direct one's attention to the benzanthracene type of molecular structure. The fluorescence spectrum was the single thread that led all through the labyrinth.*

Another batch of this crystalline material was fractionated further, in collaboration with C. L. Hewett, who joined the staff in October, 1931, under the direction of J. W. Cook, and several other compounds (2:3-benzcarbazole, chrysene, perylene) were separated from the final fractions of crystals melting at 160°. This product was taken over by Cook for identification.

The Identification and Synthesis of 3 : 4-Benzpyrene

The crystalline material, m.p. 160°, prepared from the distillate of the pitch, was of dubious homogeneity, and by means of a series of fractional crystallizations of the picrates Cook was able to isolate from it two essentially pure crystalline products (m.p. 176° and 187°). Analysis of these two compounds and their picrates showed them to be hydrocarbons uncommonly rich in carbon. Both of them, in fact, appeared to be isomeric with the highly condensed pentacyclic aromatic hydrocarbon perylene. The major component (m.p. 176°) showed in high dilution the characteristic fluorescence spectrum discussed above.

Consideration of these and other properties led Cook and Hewett to conclude that it might assist identification of these two hydrocarbons to prepare for comparison synthetic specimens of the then unknown pentacyclic hydrocarbons isomeric with perylene, 3 : 4-benzpyrene and 1 : 2-benzpyrene. This they were able to achieve by methods which, taken in conjunction with one another, established unequivocally the structures of the synthetic products. It was shown by direct comparison that 3:4-benzpyrene was identical with the strongly fluorescing major component of the crystals prepared from the pitch distillate. The synthetic preparation (m.p. 177°) was also highly carcinogenic. The synthetic 1 : 2-benzpyrene was identical with the minor component (m.p. 187°) of the original crystallate.

In 1939 the first award of the Anna Fuller Memorial Prize was made to J. W. Cook, C. L. Hewett, I. Hieger, E. L. Kennaway, and W. V. Mayneord "in recognition of their notable accomplishments in the fields of Cancer Research, specifically for the isolation and synthesis of cancer-producing hydrocarbons from coal-tar, the identification by fluorescence spectroscopy, and for the study of the biological effects of these substances."

The work described here received throughout the valuable support of the British Empire Cancer Campaign. These notes have been compiled in consultation with all five of those—F. Goulden, I. Hieger, W. V. Mayneord, J. W. Cook, and C. L. Hewett—who took part in an investigation begun 33 years ago. We all continue to be engaged in biochemistry in more or less close relation to the study of cancer.

*Hieger discovered that the active fractions all gave a deep cherry-red colour with concentrated sulphuric acid, and this test also proved quite useful in sorting out the various fractions. Of the three $C_{20}H_{12}$ hydrocarbons ultimately isolated, the active 3:4-benzpyrene was the only one to give this colour reaction.

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HYPOPHYSECTOMY IN MAN*

FURTHER EXPERIENCES IN SEVERE DIABETES MELLITUS

BY

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Whereas the introduction of insulin in the treatment of diabetes mellitus has increased the life expectancy of juvenile diabetics, this longer survival has been accompanied by an increasing incidence of diabetic vascular complications. Once these have begun they progress, leading ultimately to blindness and death, usually from renal insufficiency or cerebral haemorrhage.

In an attempt to arrest the progress of such complications when they occur we have performed hypophysectomy (Luft *et al.*, 1952, 1953, 1954, 1955). Our purpose in doing so was to eliminate those anterior pituitary factors which animal experiments have shown to possess a diabetogenic action, as we thought that these hormones might be connected with the development and/or progression of the vascular disorders. The only hypophysectomy in a case of diabetes mellitus reported previously was that of Chabanier *et al.* (1936). However, from the data given, and especially from the fact that the post-operative daily requirement of insulin in this case was 70–80 units, we are inclined to consider the operation as incomplete.

Our first case was operated on in November, 1951, and up to date 20 patients in all have been subjected to this procedure. The operative technique has already been described in detail (Luft and Olivecrona, 1953). Of the 20 hypophysectomies, 11 have been performed since

*Based on a Ciba Foundation Lecture given by Professor Olivecrona on June 15, 1955, and a communication by Dr. Luft at the Second International Congress of Diabetes at Cambridge, July 8, 1955.

TABLE I.—*Vascular Complications at Time of Hypophysectomy*

Case No.	Sex	Age (Years)	Duration of Diabetes*	Duration of Complications*	Date of Hypophysectomy	Eyes		Kidneys			Circulation	
						Vision† (R/L)	Retinopathy (R/L)	Albuminuria (g. per day)	C_{In}–$C_{P.A.H.}$‡ (ml. min./1·73 sq. m.)	Lipoid Droplets‖	Blood Pressure¶ (mm. Hg)	Calcification of Peripheral Vessels
1	M	30	17	1	Nov., 1951	0 /0	+/+	1·58	69§–	–	168–100	+
2	M	29	18	1	May, 1952	0·7/0	+/+	0·50	111–582	+	148– 97	
3	F	24	15	3	June, 1952	0·3/0·2	+/+	1·17	96–380		157–107	
4	F	30	18	5	March, 1953	0 /0	+/+	2·67	63§–226		138– 93	–
5	F	27	14	7	April, 1953	<0·1/0	+/+	3·10	47–292		154– 99	–
6	F	28	19	2	May, 1953	0·1/0·6	+/+	1·00	87–386	+	145–100	–
7	M	23	20	5	Dec., 1953	0 /<0·1	+/+	7·50	67–448		178–105	+++
8	M	31	19	2	May, 1954	0·1/0·5	+/+	2·74	69–469	+	198– 99	–
9	F	22	13	2	June, 1954	0·1/<0·1	+/+	<0·1	49–273	+	150– 87	–
10	M	31	19	2	July, 1954	<0·1/<0·1	+/+	2·00	78–448	+	160– 85	+
11	M	31	19	2	Sept., 1954	0·2/0·2	+/+	2·40	100–482	+	155– 95	++
12	F	21	14	1	Oct., 1954	0·3/0	+/+	1·57	120–573	+	150– 90	+
13	F	27	22	3	Oct., 1954	0·5/0	+/+	0·40	113–570	–	140– 93	–
14	F	24	21	2	Nov., 1954	<0·1/0·1	+/+	<0·1	128–558	+	123– 85	–
15	M	25	16	4	Dec., 1954	0·3/0·5	+/+	1·45	96–383	–	160– 97	+
16	M	24	21	4	Nov., 1954	0·3/0	+/+	0·70	94–451	+	150–100	++
17	F	25	17	1	Jan., 1955	0·1/0·5	+/+	2·31	71–476	+	150–113	+
18	F	25	17	1	Febr., 1955	<0·1/0·1	+/+	<0·1	108–475	+	135– 90	–
19	M	33	15	4	April, 1955	<0·1/0·4	+/+	1·86	85–531	+	148– 99	–
20	M	20	17	2	June, 1955	0·3/0·2	+/+	<0·1	124–869	+	115– 75	–

* From the time of their diagnosis.
† Monoyer's system (normal vision = 1·0).
‡ Clearance of inulin (C_{In}) and P.A.H. ($C_{P.A.H.}$).
§ Clearance of creatinine.
‖ Doubly refractive lipoid elements.
¶ Mean values.

July, 1954. Case 20 was operated on too recently (middle of June, 1955) to be taken into consideration when assessing the results.

Description of Cases

Details of the cases are presented in Table I. The patients consisted of 10 males and 10 females aged between 20 and 33 years. At the time of operation the duration of diabetes varied between 13 and 22 years and vascular complications had been diagnosed one to seven years earlier. Diabetic retinopathy was present in all cases. Traces of albumin were found in the urine in four cases, while the remainder showed a daily excretion of between 0.4 and 7.5 g. of protein. Doubly refractive lipoid elements were present in the urine of 13 out of 16 patients before and/or after hypophysectomy. It may be noted that in three cases (Nos. 14, 18, and 20) such elements were found, although albuminuria was minimal and the renal clearance values were within normal limits. The systolic blood pressure was below 140 mm. Hg in four cases, between 140 and 160 mm. in 11 cases, and 160 mm. or higher in another five cases. A diastolic blood pressure lower than 90 mm. Hg was recorded in four cases, between 90 and 99 mm. in 10 cases, and 100 mm. or more in the remaining six cases. Calcification of the peripheral vessels was observed on *x*-ray examination in 8 out of 18 cases (6 males and only 2 females).

Mortality (Table II)

Two of the 19 patients died within the first post-operative week; another died during the first month after operation with septicaemia following a thrombosis in one leg. A fourth patient, aged 23 years, was found at operation to have a severe generalized arteriosclerosis including the cerebral vessels, which were very brittle; after the operation he presented the clinical picture of extensive cerebral damage with progressive mental deterioration, and died six months later from a complicating pneumonia.

Of the remaining 15 patients, one died four weeks after the operation, after being for 24 hours in an epileptic state, presumably caused by a hypoglycaemia resistant to the treatment used. The same complication, when encountered in another case later on, responded well to massive doses of A.C.T.H. and cortisone and intravenous infusions of glucose.

Two further deaths occurred 15 and 19 months respectively after operation, one during a hypertensive crisis and one from renal insufficiency. In both cases there were advanced vascular complications before operation, and both had received deoxycortone acetate (D.C.A.) for many months.

TABLE II.—*Causes of Death in Seven Cases of Diabetes Mellitus after Hypophysectomy*

Case No.	Time of Survival	Cause of Death	Remarks
2	1 day	Post-operative complications	
15	3 days	,, ,,	
13	1 month	Septicaemia	
7	6 months	Arteriosclerosis	
3	1 month	Hypoglycaemia ?	No cortisone given
4	15 months	Hypertensive crisis	Received D.C.A.
5	19 ,,	Nephropathy	,, ,,

Post-operative Management

Substitution therapy after the initial post-operative period included the administration, in addition to insulin, of thyroid hormone in a daily dose equivalent to 100–150 μg. of thyroxine, oestrogenic or androgenic hormones, and adrenal cortical hormones. In the first six cases operated on (including two with a fatal outcome) D.C.A. was given as adrenal cortical substitute for a considerable time in order to avoid the diabetogenic substance cortisone. Observations in these first cases suggested that D.C.A. was harmful. In this connexion it should be mentioned that D.C.A. is known to have an unfavourable effect on already damaged blood vessels, therefore cortisone has been the only adrenal cortical substitute given during the last eighteen months, the daily dose varying between 10 and 15 mg. On the maintenance therapy outlined above the general condition of the patients is good and some of them have returned to their previous occupations.

The dietary regimen after stabilization of the condition has been on the basis of 1,400–1,700 calories daily with a carbohydrate intake of 120–150 g. for women, and 1,600–2,000 calories daily with a carbohydrate intake of 150–180 g. for men. With this regimen the daily requirement of long-acting insulin (P.Z.I. or lente insulin) varied between 8 and 24 units—approximately one-fourth to one-third of the pre-operative dosage. The daily sugar excretion has varied usually between zero and 80 g. Control of the diabetes has purposely not been very rigorous, in order to avoid possible hypoglycaemic attacks. In none of the cases have clinical signs or laboratory evidence of acidosis been observed.

Assessment of Results

The therapeutic results in the 12 surviving cases will be evaluated with respect to the condition of the circulatory system, the kidneys, and the eyes. The period of observation up to July 1, 1955, ranged from 3 to 43 months. The question whether the hypophysectomy was complete cannot be answered at present, but the results of the tests performed are consistent with the view that the operation was incomplete in only one case (No. 11).

Circulation

The effect of the operation on the blood pressure is shown in Fig. 1. In 10 of the 12 cases the systolic pressure was above 140 mm. and in seven of these the diastolic pressure was higher than 90 mm. Hg. A fall in the systolic pressure was observed after the operation. During the first post-operative year a systolic pressure not exceeding 140 mm. was reached in all cases save one. A tendency for the

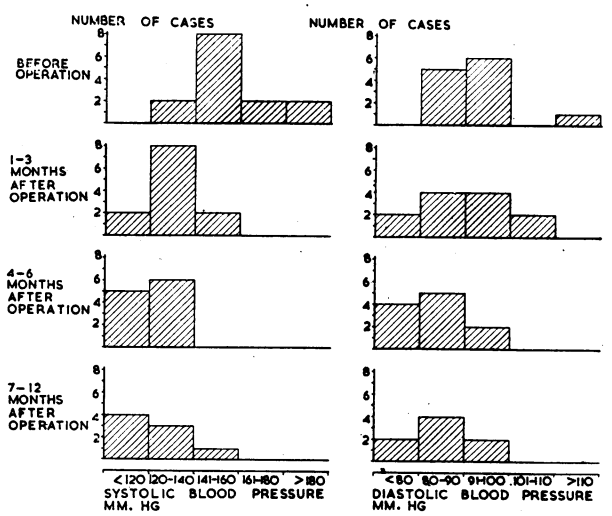

FIG. 1.—Effect of hypophysectomy on blood pressure.

diastolic pressure to decrease was also noticeable. Only two of the cases have been observed for more than a year, and the changes in blood pressure in these are shown in Fig. 2. The patients have now, 43 and 25 months respectively after the operation, regained the pre-operative blood pressure after an interval of normal tension. Both cases belong to the group given D.C.A.

In Table III are shown the changes in heart volume in nine cases. From this it can be seen that the heart tends to decrease in size after hypophysectomy.

In those cases in which calcification of the peripheral vessels was found before operation such calcification was still present at subsequent follow-up examinations. In no other cases has calcification appeared post-operatively.

Although an increased capillary fragility is often encountered in diabetics with vascular disease, in all the cases except one in which this was estimated the capillary fragility was normal after the operation.

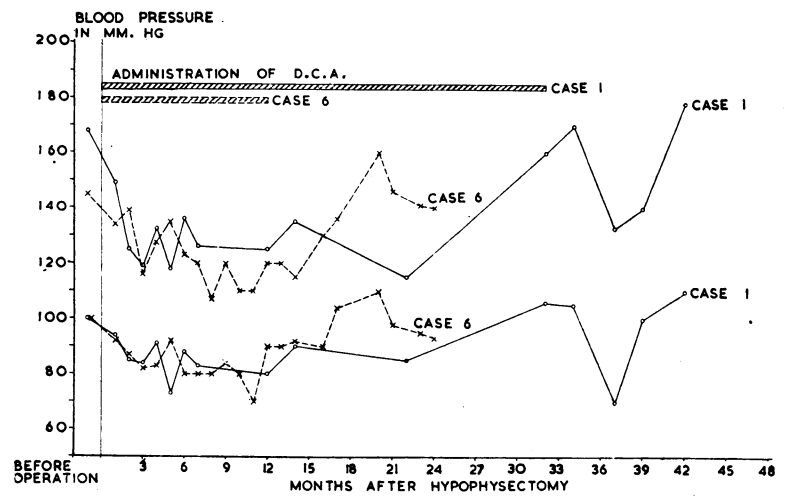

FIG. 2.—Changes in blood pressure in Cases 1 and 6 during administration of D.C.A.

TABLE III.—*Changes in Heart Volume*

Case No.	Time of Observation (Months)	Size of Heart (ml. per sq. metre surface area)		
		Before Operation	Last Examination	Difference %
1	42	310	350	+13
8	10	450	360	−20
9	12	370	310	−16
11	5	320	330	+ 3
12	5	280	280	± 0
14	5	300	220	−27
17	5	320	260	−19
18	2	430	330	−23
19	2	360	320	−11

TABLE IV.—*Changes in Albuminuria*

Case No.	Albuminuria (g. per day)		
	Before Operation	Last Control Test	Time After Operation (Months)
1	1·58	1·38	42
6	1·00	1·00	24
7	7·50	1·78	6
8	2·74	1·73	10
9	<0·10	<0·10	12
10	2·0 (?)	0·85	9
11	2·40	1·79	7
12	1·57	0·57	6
14	<0·10	<0·10	7
16	0·70	Nil	3
17	2·31	0·95	4
18	<0·10	<0·10	5
19	1·86	1·29	2

TABLE V.—*Occurrence of Doubly Refractive Lipoid Elements in the Urine*

Case No.	Before Operation		After Operation	
	No. of Examinations	Positive Results	No. of Examinations	Positive Results
1				0
6				2
8			7	7
9			7	1
10			12	8
11			13	1
12	2	2	21	5
14	7	1	21	0
16	2	1	9	2
17	2	2	12	6
18	5	2	12	0
19	3	2	5	0

Renal Function

It is of course difficult to say in just how many cases a diabetic nephropathy was present at the time of operation. In all cases except No. 1 lipoid crystals were observed in the urine at some time before and/or after the operation. In 9 of the 12 cases albuminuria in more than a trace was present; in the remaining 3 cases a trace of albumin was found.

The effect of the operation on the albuminuria is given in Table IV. A definite decrease was observed in nearly all cases. Table V shows the effect of the hypophysectomy on the occurrence of lipoid crystals. These were absent from the urine after the operation in four cases, in three of which they were present pre-operatively.

The effective renal plasma flow as measured by *p*-aminohippurate (P.A.H.) remained practically unchanged after the operation (Fig. 3). In contrast, the glomerular filtration rate (inulin clearance) markedly decreased immediately after the operation and remained at this low level for the rest of the period of observation. Consequently a marked decrease in the filtration fraction was induced by the operation. The decrease in inulin clearance is most probably due to the ablation of the hypophysis, and cannot be regarded as a sign of progression

of the renal changes. Analogous decreases in the glomerular filtration rate were observed by us after hypophysectomy in patients suffering from cancer without demonstrable renal disease. The fact that the inulin clearance remained unchanged after the initial post-operative decrease supports

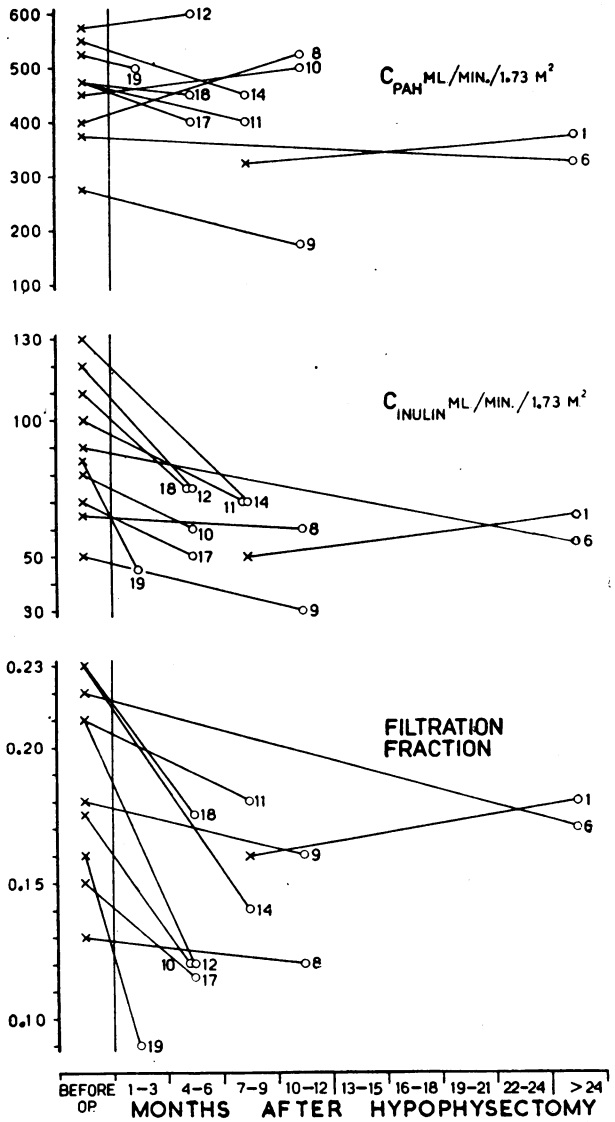

FIG. 3.—Changes in clearance of P.A.H. and of inulin and infiltration fraction.

the above explanation of the reduction observed. The decrease in the filtration fraction together with the unchanged renal plasma flow can be taken as a sign of a lowering of tonus of the vessels of the glomeruli, which in turn can be considered as a favourable effect of the operation on the renal circulation.

The non-protein nitrogen content of the blood was within normal limits before as well as after the operation.

From the above results it may be concluded that there were no signs of progression of the diabetic renal disease after the operation in our 12 cases. Our data at present do not permit any conclusions as to improvement in the condition of the kidneys.

Eyes

All the cases operated on had advanced diabetic retinopathy. As shown in Table VI, the visual acuity, as measured by Monoyer's system, remained on the whole unchanged after hypophysectomy. In three patients the vision of one eye decreased owing to acute retinal haemorrhage;

TABLE VI.—*Changes in Visual Acuity and Capacity*

Case No.	Time of Observation (Months)	Visual Acuity*				Patients' Statements		
		Right Eye		Left Eye		Ability to Read†		General
		Before Operation	Last Control	Before Operation	Last Control	Before Operation	Last Control	
1	43	Patient blind						
6	24	<0·1	0·1	0·6	0·4	+++	++++	Better
8	13	0·7	<0·1	0·5	0·9	+++	++++	,,
9	12	<0·1	0·1	0·1	0·1	+	++	,,
10	11	<0·1	<0·1	<0·1	<0·1	++	+	Worse
11	9	0·2	0·2	0·2	0·2	++	++	Unchanged-worse
12	8	0·3	0·1	0·0	<0·1	+	++	Better
14	8	<0·1	0·1	<0·1	<0·1	+	++	,,
16	7	0·3	0·3	<0·1	<0·1	++	++	Unchanged
17	6	<0·1	0·5	0·5	<0·1	++	+++	Better
18	5	<0·1	<0·1	0·1	0·5	+	++	,,
19	3	<0·1	<0·1	0·4	0·7	+++	+++	Unchanged

* Measured by Monoyer's system.
† + Unable to read.
++ Able to read with magnifying-glass.
+++ Able to read but with difficulty.
++++ Normal ability to read.

in these cases there was a comparable increase in visual acuity in the other eye. In the remaining cases the visual acuity either improved or remained unchanged. As to the patients' subjective impression of their visual capacity, an improvement was reported by seven, no change by four (one of whom was blind before the operation), and worsening by one. These changes have been roughly assessed by the patients' reading ability (see Table VI).

In 10 cases the eye-ground changes have been followed regularly, and permanent records obtained by colour photography, this being impossible in the remaining cases owing to the presence of cataracts. In one case (No. 10) a marked progression of the diabetic retinopathy was observed after a short period of improvement, and started at a time when the patient had an exacerbation of rheumatoid arthritis. (This is the same patient who reported a deterioration in visual capacity.) In the remaining nine cases no definite signs of progression were observed; this leaves out of account three instances of acute haemorrhage, apparently arising from newly formed vessels already present before the operation. On the contrary, decrease in the formation of new vessels was observed in five cases. In Case 6 before operation there was in the right fundus very advanced retinopathy with marked haemorrhages, new vessel formation, exudation, and proliferation. One year later the newly formed vessels had disappeared and exudates and proliferations markedly diminished. This improvement has been maintained to date, 24 months after the operation. In the left eye, in which only exudates and haemorrhages were present pre-operatively, these have decreased significantly.

From the above findings it can be concluded that in all cases save one, except for occasional retinal haemorrhages, no symptoms or signs of progression of the diabetic retinopathy were evident. On the contrary, improvement in visual capacity and/or eye-ground changes were noted in most cases.

Summary and Conclusions

Hypophysectomy has been performed in an attempt to arrest the progress of the vascular complications of diabetes, the aim being to eliminate those anterior pituitary factors shown to have a diabetogenic action. Results in 20 patients aged between 20 and 33 years are presented and evaluated. In all cases there was diabetic retinopathy; blood pressure was generally raised and albuminuria and proteinuria were present. Death occurred in seven cases between one day and 19 months of operation. Patients were followed up for 3 to 43 months. Substitution therapy consisted in the administration of thyroxine, oestrogens or androgens, and adrenocortical hormone or D.C.A. Women received a

diet containing 1,400–1,700 calories daily, and men one of 1,600–2,000 calories, together with a daily maintenance dose of 8–24 units of a long-acting insulin.

In the surviving cases the operation was followed by a fall in blood pressure and a decrease in heart volume. Where calcification of peripheral vessels existed before operation this was not affected, but no calcification occurred in other cases. Capillary fragility was normal. A definite decrease in albuminuria and in glomerular filtration rate was achieved, but the effective renal plasma flow remained unchanged. This can be considered to indicate a favourable effect on the renal circulation. No signs of progression of the renal disease were observed, though no conclusions are drawn as to improvement in the condition of the kidneys. The visual capacity improved in some cases, and the retinal changes did not progress further.

The limited period of observation and the small number of cases do not permit conclusions as to the therapeutic value of hypophysectomy for the vascular complications of diabetes, but results so far obtained are encouraging.

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PRESENT POSITION OF THE CHEMOTHERAPY OF BACTERIAL INFECTIONS*

BY

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No one will dispute that the "present position" of this subject is exceedingly complex. As the result of two major discoveries, the first of which—that of the sulphonamides—was made twenty years ago, an apparently unending series of potent new antibacterial drugs is being produced. If we look at the chronological sequence of these discoveries (Table I) it is seen that the two main trends overlap: further new sulphonamides and other synthetic compounds have been introduced since the beginning of the antibiotic era. It is scarcely surprising that some of these drugs should have been comparatively neglected, and there can be very few people with definite and well-supported views about the relative merits of the later sulphonamides. I was so impressed recently by the lack of information on this subject that I did a series of tests of the *in vitro* antibacterial activity of "gantrisin" and "elkosin" in comparison with sulphathiazole and sulphadimidine against four types of organism causing urinary infections. I found singularly little difference between them, and, although of course they may differ in other desirable qualities, it seems that by this kind of test one good sulphonamide is very like another.

*Paper read to the First Plenary Session of the Joint Annual Meeting of the British Medical Association, Canadian Medical Association, and Ontario Medical Association, Toronto, 1955.

TABLE I.—*Antibacterial Chemotherapy: Sequence of Discoveries* 1935–55

	Synthetic Compounds	Antibiotics
1935	Prontosil	
1936	Sulphanilamide	
1938	Sulphapyridine	
1939	Sulphathiazole	
1940	Sulphadiazine	Penicillin
1942	Sulphadimidine	
1943	Sulphasomidine (elkosin)	
1944		Streptomycin
1945	*p*-Aminosalicylic acid	Bacitracin
1947	Sulphafurazole (gantrisin)	Polymyxin. Chloramphenicol
1948		Chlortetracycline
1949		Neomycin
1950		Oxytetracycline
1952	Isoniazid	Erythromycin
1953		Tetracycline

Among the antibiotics, on the other hand, no two are alike, apart from the close similarity between the tetracyclines. For each there is a whole series of different indications, which can only be expressed adequately by a detailed table of bacterial sensitivities. It is far too much to expect that the clinician should carry such a mass of information in his head, and the result of this is that a good deal of his use of antibiotics tends to be empirical. Not only may he be undecided in his choice of an antibiotic, but having chosen it he may still be uncertain in what form to use it.

The number of "dosage forms" of penicillin listed in a well-known American work is 46. It is true that some of them, such as toothpaste and suppositories, are trivial; others are mixtures with other antibiotics, with little merit except novelty; but for the single legitimate purpose of achieving a systemic effect the clinician has to choose between various forms of oral medication and the injection of preparations which in a given dose will exert an effect for either a few hours, one to two days, four to five days, or two to three weeks. The blood levels attained vary inversely with the duration of effect (Fig. 1). There are special indications for soluble penicillin on the one hand, and for very long-acting preparations of it on the other, but for the treatment of everyday acute infections the relative merits of freely soluble and depot preparations are still arguable. I am inclined to subscribe to Eagle's doctrine (Eagle *et al.*, 1953), which, as I understand it, favours longer-acting preparations, but the late F. R. Selbie, shortly before his death last year, thought it necessary to re-explore the question experimentally, and reached a somewhat different conclusion (Selbie, 1954).

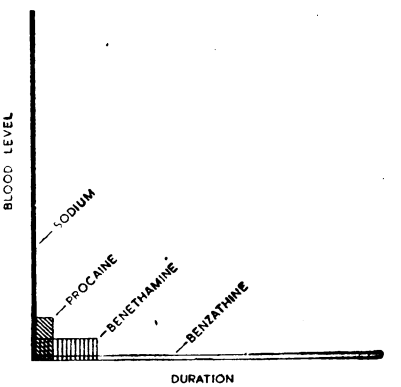

FIG. 1.—Relationship between blood concentration and duration of effect following single doses of four forms of penicillin (schematic).

Indications for Different Antibiotics

I propose to consider only the use of antibiotics, and in the first place the indications for some of them. Apart from